FORMATION OF PARAMETRIC IMAGES IN POSITRON EMISSION TOMOGRAPHY USING A CLUSTERING-BASED KINETIC ANALYSIS WITH STATISTICAL CLUSTERING *

Yuichi KIMURA†, Yasuhiro NOSHI‡, Keiichi ODA† and Kenji ISHII†
† Positron Medical Center, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan
‡ Major in Integrative Bioscience and Biomedical Engineering, Waseda University, Tokyo, Japan

Abstract– **A method is proposed for forming parametric images in positron emission tomography, using clustering kinetic analysis. To overcome the dual problems experienced in voxel-based data, of signal noise and the very long computational time, the data are clustered before parameter estimation, and then an estimation procedure is applied to the averaged data in each cluster. Using this algorithm, PET data are optimally clustered, depending on the noise that is present, by hierarchically applying a statistical-clustering algorithm based on Mixed Gaussian model. In a computer simulation, the proposed method correctly clustered noise-contaminated data. Applying the proposed algorithm to ^{18}F–FDG clinical data, physiologically acceptable parametric images of glucose metabolism in a brain were obtained in a practical calculation time.**

Keywords — positron emission tomography, kinetic analysis, compartment model, statistical clustering, Mixed Gaussian model

I. INTRODUCTION

In positron emission tomography (PET), an isotope-labeled radio-pharmaceutical is administered, and its spatial distribution is measured using computed tomography. In this way, some functionalities in living tissue can be derived as an image. Detailed information about physiological functions is available if the history of the concentration of the accumulated radio-pharmaceutical in the target tissue can be measured (tissue time activity; tTAC). This can be done by performing multiple PET measurements following the injection, and is known as a kinetic analysis. Usually kinetic analysis is applied in a region-of-interest (ROI) base, but if kinetic analysis is applied in a voxel base, more precise spatial information can be obtained. However, voxel-based kinetic-analysis has two drawbacks: poor signal-to-noise ratio in the voxel-based tTACs, and a very large calculation time. To address these problems, a method called clustering analysis for kinetics (CAKS) has been described [1] and [2]. This applies to both the two-compartment-two-parameter model (2C2K-model) and the three-compartment-three-parameter model (3C3K-model). In the CAKS for the 3C3K-model, voxel-based tTACs are categorized by projections spawned by the first and second principal components calculated from a principal-component analysis (PCA) applied to the tTACs of all voxels.

The concept of CAKS is that normalized tTACs with the same shape can be expected to have the same kinetic parameters. Therefore, noise can be reduced in an averaged tTAC in a cluster with the same parameter. Because this estimation process is applied not in a voxel-by-voxel mode, but in a cluster-by-cluster mode, the number of invoked algorithms used in the estimation can be reduced, and a shorter calculation time can be achieved.

In CAKS, clustering of projected points defined by the principal components (PC) is important. A statistical clustering algorithm based on the Mixed-Gaussian model will be utilized in this study of the 3C3K (K_1, k_2, k_3) model.

II. METHOD

A. Clustering Analysis for Kinetics

The CAKS algorithm for the FDG 3C3K model is introduced. Eqn.1 is the analytic solution for the FDG 3K model [3].

$$C(t) = \frac{K_1}{k_2 + k_3}\left[k_3 + k_2 \exp\left\{-(k_2 + k_3)t\right\}\right] \otimes C_p(t) \quad (1)$$

assuming k_4 is zero; where $C(t)$ and $C_p(t)$ denote the tTAC, and the plasma time-activity curve (pTAC), respectively. K_1 and k_2 summarize the rates of tracer transportation from plasma to the tissue-free FDG pool, and its reverse direction; k_3 is a rate constant describing the conversion rate from FDG to FDG–6–PO_4. In the clustering method, K_1 is considered to be a scaling factor, whereas k_2 and k_3 describe the shape of the tTAC. In order to ignore K_1 for clustering, a tTAC with n frames is treated as an n-element vector, and normalized by its amplitude according to Eqn.2.

$$C'(t) = \frac{C(t)}{\int_0^{T_E} C(\tau)d\tau} \quad (2)$$

where C, C' and T_E denote a voxel-based tTAC, a normalized tTAC, and the time of the final frame, respectively. Next, PCA is performed on all the normalized tTACs in order to determine n principal components. Projection of the vectors onto a feature space defined by the first two PCs can be utilized for clustering. The statistical clustering method of the Mixed-Gaussian Model is applied here to achieve reliable clustering.

*This work is partly supported by Grant-in-Aid for Scientific Research (C) No. 13670977 from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

†kimura@pet.tmig.or.jp

Report Documentation Page

Report Date	Report Type	Dates Covered (from... to)
25 Oct 2001	N/A	-

Title and Subtitle Formation of Parametric Images in Positron Emission Tomography Using a Clustering-Based Kinetic Analysis With Statistical Clustering	**Contract Number**
	Grant Number
	Program Element Number
Author(s)	**Project Number**
	Task Number
	Work Unit Number
Performing Organization Name(s) and Address(es) Positron Medical Center Tokyo Metropolitan Institute of Gerontology Tokyo, Japan	**Performing Organization Report Number**
Sponsoring/Monitoring Agency Name(s) and Address(es) US Army Research, Development & Standardization Group (UK) PSC 802 Box 15 FPO AE 09499-1500	**Sponsor/Monitor's Acronym(s)**
	Sponsor/Monitor's Report Number(s)

Distribution/Availability Statement
Approved for public release, distribution unlimited

Supplementary Notes
Papers from 23rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society, October 25-28, 2001, held in Istanbul, Turkey. See also ADM001351 for entire conference on cd-rom. , The original document contains color images.

Abstract

Subject Terms

Report Classification unclassified	**Classification of this page** unclassified
Classification of Abstract unclassified	**Limitation of Abstract** UU

Number of Pages
3

B. Mixed Gaussian Model (MGM)

There is a correspondence between a pair of (k_2, k_3) and the point in the feature space. However, because of noise in the measured tTAC, the actual point in the feature space deviates from its true location. This fluctuation is assumed to have a Gaussian distribution, and its mean (μ) and covariance (Σ) are estimated using the EM algorithm [4].

The projected point onto the feature space is denoted as a two-dimensional vector $\boldsymbol{x}$, with a probability $p(\boldsymbol{x})$, which is assumed to be the sum of the occurrence probabilities of each cluster.

$$p(\boldsymbol{x}) = \sum_{j}^{M} p(\boldsymbol{x}|j)P(j) \tag{3}$$

where $M, p(\boldsymbol{x}|j), \text{and} P(j)$ are the number of clusters, the probability of generating the value $\boldsymbol{x}$ from the j'th cluster, and the existence probability of the cluster, respectively. Because a Gaussian distribution is assumed, we can have Eqn.4.

$$p(\boldsymbol{x}|j) = \frac{1}{2\pi|\Sigma_j|^{1/2}} \exp\left\{-\frac{1}{2}(\boldsymbol{x}-\mu_j)^T\Sigma_j^{-1}(\boldsymbol{x}-\mu_j)\right\} \tag{4}$$

$P(j|\boldsymbol{x})$, which describes the probability of $\boldsymbol{x}$ belonging to the j'th cluster, is estimated according to Eqn.3 and Eqn.4 combined with Bayes' theorem **??**.

$$P(j|\boldsymbol{x}) = \frac{p(\boldsymbol{x}|j)P(j)}{p(\boldsymbol{x})} \tag{5}$$

Finally, for each $\boldsymbol{x}$, the cluster which has the highest probability is determined to be the associated cluster.

The number of voxels in a cluster should be 100 or more so as to have adequate noise reduction. Since some thousands of voxels are contained in a brain region in a typical clinical PET, the total number of clusters exceeds 500. It is difficult and impractical to estimate all of parameters of MGM in such a large model. A hierarchal clustering procedure is proposed to overcome this problem, in directly driving of the MGM algorithm. Firstly, all the voxels are clustered into four categories, then each cluster is further clustered into four categories, and so on. If these steps are repeated three times the final number of cluster will be 64. In each step, the sample mean and covariance are calculated, and the mean points for the next MGM step are given using these values. Only the prior probability of $P(j)$ and the covariance of Σ_j are estimated.

All the programs are implemented in MATLAB ver. 5 on a Sun workstation.

C. Computer Simulation

To make sure that the hierarchal algorithm can be properly clustered, a computer simulation was designed. The centers of the 16 clusters are placed at $(0,0), ..., (0,3), (1,0), ..., (3,3)$, and Gaussian random values were generated from each center with a covariance of $\begin{pmatrix} 0.5 & 0 \\ 0 & 0.5 \end{pmatrix}$. The number of data for each cluster was 100. The MGM algorithm was applied to this data set, and the estimated parameters were compared with their true values.

D. Clinical Data

The CAKS algorithm was applied to typical FDG clinical data to form parametric images of $K_1, Dv(= K_1/k_2), k_3, K_i(= k_2k_3/(K_1 + k_3))$. These images were obtained from an Alzheimer patient using HEADTOME–IV (Shimadzu Corp, Japan) with 128-by-128 voxels and seven slices, with arterial blood sampling and transmission scan. Corrections for dead-time and attenuation were applied before reconstruction using ordinal filtered back-projection algorithm with 8 mm as FWHM.

III. RESULTS

A. Validation of Hierarchal MGM Clustering

Fig. 1 shows the generated data points, and the true and estimated centers with $\cdot$, $\times$ and $\circ$, respectively. The mean distance between the true and estimated centers is 0.066. The hierarchal algorithm was able to derive acceptable estimates, but if the MGM algorithm was applied directly to all the simulation data, it did not converge.

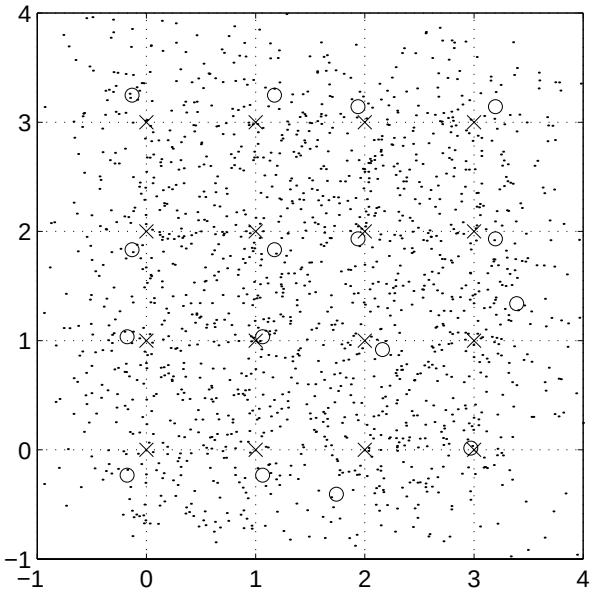

Fig.1 : Simulation data and estimates

B. Clinical Parametric Image

Estimated clinical parametric images are show in Fig. 2. Physiologically, K_1 reflects the cerebral regional blood flow (CBF) and the CBF is different for gray and white matter (GM and WM). There is clear structure in the brain in K_1, and the K_1 parametric image seems to be reasonable. Notice also that the same thing arises in the K_i image because of a large difference in glucose utilization between GM and WM. The interesting aspect of the k_3 image is that there is no difference between GM and WM. Further investigation will be required to determine the meaning of this.

The calculation time was five minutes for clustering, and one minute for estimation.

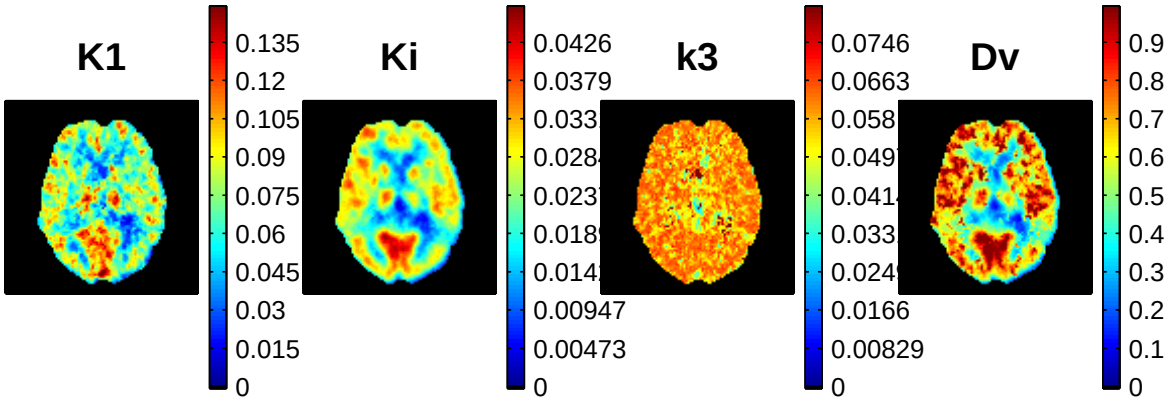

Fig.2 : Clinical parametric images

IV. DISCUSSION AND CONCLUSION

Voxel-based kinetic-analysis to form parametric images in PET has the potential to derive spatial distribution of some functionalities in living human tissue. However, because of the high noise-level in voxel-based tTAC, and the long calculation time, derivation of a parametric image is not practical. CAKS is one approach to overcome these problems, and a statistical algorithm for clustering was proposed in this study. In CAKS, every voxel-based tTAC is projected onto the feature space defined by the first and second principal components in which a large noise level is noticeable. The Mixed-Gaussian model has attractive features, in that it tries to estimate the statistical properties of the projected tTAC to decide the boundary for statistical clustering. By combining the MGM estimation with the EM algorithm, a robust and quick convergence can be attained. In a simulation study, the estimated clusters correspond well to their true location. If this clustering algorithm is applied to a clinical image, the derived parametric images are physiologically reasonable. The calculation time for the whole process to form parametric images is approximately 10 minutes using an ordinal UNIX computer. We conclude that CAKS with hierarchal clustering and MGM, is a practical way to extract more information about functionality from PET.

References

[1] Yuichi Kimura, Hongbing Hsu, Hinako Toyama, Michio Senda, and Nathaniel M. Alpert, "Improved signal-to-noise ratio in parametric images by cluster analysis," *NeuroImage*, vol. 9, no. 5, pp. 554–561, May 1999.

[2] Yuichi Kimura, Kenji Ishii, Michio Senda, and Nathaniel M. Alpert, "Formation of FDG parametric images based on clustering and principal components," in *The Journal of Nuclear Medicine Abstract Book Supplement*, 2000, vol. 41, p. 397, St. Louis.

[3] Sung-Cheng Huang, Michael E. Phelps, Edward J. Hoffman, Klear Sideris, Carl J. Selin, and David E. Kuhl, "Noninvasive determination of local cerebral metabolic rate of glucose in man," *American J. of Physiology*, vol. 238, no. 1, pp. E69–E82, Jan. 1980.

[4] Christopher M. Bishop, "Mixture models," in *Neural Networks for Pattern Recognition*, pp. 59–73. Oxford University Press, 1995.